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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/612,463	07/01/2003	Francisco Cruz	67-97A	3099

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GREENLEE WINNER AND SULLIVAN P C
4875 PEARL EAST CIRCLE
SUITE 200
BOULDER, CO 80301

EXAMINER	
SOROUSH, LAYLA	
ART UNIT	PAPER NUMBER
1617	
MAIL DATE	DELIVERY MODE
08/05/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/612,463	CRUZ ET AL.	
	Examiner	Art Unit	
	LAYLA SOROUSH	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 April 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-3 and 5-13* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3 and 5-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on April 28, 2008 has been entered. Claims 1-3, 5-13 are pending.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, and 5-7 rejected under 35 U.S.C. 103(a) as being obvious over Craft et al. (Temporal Parameters of Desensitization to Intravesical Resiniferatoxin in the Rat, Physiol. Behave. Vol. 56, No. 3, pp. 479-486, 1994 - IDS) in view of Nordhauser et al. (Sterilization of Drugs and Devices: Technologies for the 21st Century, Forward, 1998).

Craft et al. teaches intravesicular instillation administration of resiniferatoxin at 0.33uM concentration. The resiniferatoxin was dissolved in ≤ 2

% ethanol to which 1% Tween-80 (nonoionic detergent (polysorbate 80)) and saline were added (see page 480, Drugs). The concentration limitation is met by the teachings of the reference. Further, the prior art reads on the limitation of a first and second container; because the compounds must necessarily be contained in containers, and the teaching that the resiniferatoxin was dissolved in ethanol and Tween-80 and saline were added supports the fact that there are separate containers, one holding the resiniferatoxin and the other diluents.

The reference does not specifically teach a sterile dose of the therapeutic compound.

Nordhauser et al. teaches that since 1991, the FDA has required terminal sterilization of all aqueous parenteral drugs. Sterilization of pharmaceuticals is to make a drug product that lacks viable microorganisms capable of reproduction in the drug product itself or after injection into a patient.

It would have been obvious to one of ordinary skill in the art at the time of the invention to sterilize the drug. The motivation to sterilize the drug comes from the teachings of Nordhauser et al. that the FDA has required terminal sterilization of all aqueous parenteral drugs. Sterilization of pharmaceuticals is to make a drug product that lacks viable microorganisms capable of reproduction in the drug product itself or after injection into a patient. Hence, a skilled artisan would have reasonable expectation of successfully producing a sterile parenteral drug that lacks viable microorganisms capable of reproduction in the drug product itself or after injection into a patient.

The recitation wherein the compound is "compatible with bladder mucosa and does not cause meaningful pain or irritation to the patient when administered" is an intended use and does not receive patentable weight in composition claims.

Claims 2 and 3 are rejected under 35 U.S.C. 103(a) as being unpatentable over Craft et al. ((1)Temporal Parameters of Desensitization to Intravesical Resiniferatoxin in the Rat, Physiol. Behave. Vol. 56, No. 3, pp. 479-486, 1994 - IDS) and Nordhauser et al. (Sterilization of Drugs and Devices: Technologies for the 21st Century, Forward, 1998), as applied to claims 1, 5, and 6-7 above, and in view of Blumberg (US Pat No 4,939,149).

Craft et al. and Nordhauser et al. are as discussed above.

Craft et al.(1) does not teach the specific concentration and the amounts of the components as recited in claims 2 and 3.

Blumberg ('149) teaches "The desirable dose of the compounds of the present invention varies with the subject, drug form, method and period of administration. However, in order to obtain desirable effects, generally it is recommended to administer $0.1x10^{-3}$ to $5x10^{-2}$ mg/kg, preferably $0.1\ x10^{-3}$ to $5.\ x10^{-3}$ mg/kg, body weight of the compounds of the present invention for single application, or less upon multiple application. In terms of composition, compounds should be present between. 0.0001 to 10% by weight, preferably

0.0001 to 1% by weight." Based on the average weight of human (60 kg) the concentration of the active compound is preferably between 0.01-0.5 uM (column 5 lines 25-40). The RTX compounds were administered in 10% ethanol, 10% Tween-80/ 80% physiological saline solution unless otherwise indicated (column 6, lines 5-16). Blumberg ('149) teaches "RTX, the active ingredient of the present invention, can be made into pharmaceutical compositions by combination with appropriate medical carriers or diluents. The compounds of the present invention may be formulated into preparations for injections by dissolving, suspending or emulsifying them in aqueous solvents such as normal saline, Dextrose 5%, or non-aqueous solvent, such as vegetable oil, synthetic aliphatic acid glycerides, esters of higher aliphatic acids or propylene glycol; and if desired, with conventional additives such as solubilizers, isotonic agents, suspending agents, emulsifying agents, stabilizers and preservatives. For example, RTX can be dissolved in oils, propylene glycol or other solvents commonly used to prepare injectable solutions. Suitable carriers include physiological saline, polyethylene glycol, ethanol, sesame oil, cremophor and isopropyl myristate."

It would have been obvious to one of ordinary skill in the art at the time the invention was made to manipulate specific concentration, the amounts of the components parameters, and modify a carrier. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). The motivation to change the amounts and

concentration is because they are deemed to be manipulatable parameters practiced by an artisan to obtain the best possible pharmaceutical results. The motivation to modify the carrier is because Blumberg ('149) teaches useful carriers include physiological saline, polyethylene glycol, ethanol, sesame oil, cremophor and isopropyl myristate in injectables. Hence, a skilled artisan would have reasonable expectation of successfully producing a stable injectable comprising polyethylene glycol.

Claims 8-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Craft et al. (Temporal Parameters of Desensitization to Intravesical Resiniferatoxin in the Rat, Physiol. Behave. Vol. 56, No. 3, pp. 479-486, 1994 - IDS) and and Nordhauser et al. (Sterilization of Drugs and Devices: Technologies for the 21st Century, Forward, 1998) as applied to claims 1-3, 5-7, and further in view of Ebert (US Pat 2,182,075).

Craft et al. and Nordhauser et al. are as discussed above.

The reference does not teach buffering salts as recited in claims 8-10.

Ebert teaches buffering materials are used in an injectable composition to adjust the pH of their solution to about 7-7.4.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to employ a buffering material. The motivation to make such an incorporation is because the reference teaches that injections are preferably adjusted in pH and said buffering material are used in compositions to adjust the

pH of their solution to about 7-7.4. Additionally the reference teaches the buffering salts are used to avoid irritation. A skilled artisan would therefore, have reasonable expectation of producing a composition with a pH of about 7-7.4 to avoid irritation.

Claims 11-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Craft et al. ((1)Temporal Parameters of Desensitization to Intravesical Resiniferatoxin in the Rat, Physiol. Behave. Vol. 56, No. 3, pp. 479-486, 1994 - IDS), Nordhauser et al. (Sterilization of Drugs and Devices: Technologies for the 21st Century, Forward, 1998), and Blumberg (US Pat No 4,939,149), as applied to claims 1-3, 5, and 6-7 above, and further in view of Mookherjee et al. (US 4145354 A).

Craft et al., Nordhauser et al., and Blumberg are as discussed above.

The references do not teach the specific stabilizer citric acid or the stabilizers of claim 13.

However, Mookherjee et al. teaches stabilizers include preservatives, e.g., sodium chloride; antioxidants, e.g., calcium and sodium ascorbate, ascorbic acid, butylated hydroxyanisole (mixture of 2- and 3-tertiary-butyl-4-hydroxyanisole), butylated hydroxy toluene (2,6-di-tertiarybutyl-4-methyl phenol), propyl gallate and the like and sequestrants, e.g., citric acid.

It would have been obvious to one of ordinary skill in the art at the time of the invention to incorporate a stabilizer in the composition. The motivation to make such an incorporation is because (1) Blumberg ('149) teaches " "RTX, the

active ingredient of the present invention, can be made into pharmaceutical compositions by combination with appropriate medical carriers or diluents. The compounds of the present invention may be formulated into preparations for injections by dissolving, suspending or emulsifying them in aqueous solvents such as normal saline, Dextrose 5%, or non-aqueous solvent, such as vegetable oil, synthetic aliphatic acid glycerides, esters of higher aliphatic acids or propylene glycol; and if desired, with conventional additives such as solubilizers, isotonic agents, suspending agents, emulsifying agents, stabilizers and preservatives." Hence, a skilled artisan would have reasonable expectation of successfully producing the desired stabilization of RTX by incorporation of preservatives such as citric acid and ascorbic acid.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an

invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-3 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 7-9, 11, and 13 of U.S. Patent Application No. 09/138,448. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the co-pending application recites A method for alleviating symptoms of neurogenic urinary dysfunction comprising administering by intravesicular instillation to a human patient having said symptoms a therapeutically effective concentration in the range from 0.05 uM to 2.0 mM of a compound selected from the group resiniferatoxin, tinyatoxin, 20-homovanillyl-mezerein or 20-homovanillyl-12-deoxyphorbol-13-phenylacetate in a physiologically compatible solvent, said concentration being a concentration that does not cause meaningful burning or irritation to said patient, whereas the instant claims are A kit for intravesicular instillation comprising, a first container containing a unit dose of a therapeutic compound selected from the group resiniferatoxin, tinyatoxin, 20-homovanillyl-mezerein or 20-homovanillyl-12-deoxyphorbol-13-phenylacetate in a solution concentrate or dry powder form and a second container containing a physiologically compatible diluent capable of dissolving and maintaining in solution the therapeutic compound, the volume of said diluent being sufficient for intravesicular instillation of the unit dose and providing a concentration of the

therapeutic compound of from 0.05 uM to 2.uM upon mixing the diluent with the therapeutic compound, and means for combining the diluent with the stock solution or lyophilized powder under sterile conditions. It would be obvious to one of ordinary skill in the art to employ the I.V. instillation kit herein containing a unit dosage of the active compound and the solvent. The motivation to make such an incorporation is because the same active compound (resiniferatoxin) and the same solvents are taught in an intravesicular instillation. Hence, a skilled artisan would have a reasonable expectation of successfully producing the same.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Response to Arguments

Applicant's arguments filed April 28, 2008 have been fully considered. The response to the arguments is as discussed below:

Applicants' main argument is that the composition of Craft and Blumberg cause pain and burning sensation whereas the composition of the claimed invention does not cause meaningful pain or irritation to the patient. The Examiner's contention remains that the recitation wherein the compound is "compatible with bladder mucosa and does not cause meaningful pain or irritation to the patient when administered" is an intended use and does not receive patentable weight in composition claims.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Layla Soroush whose telephone number is

(571)272-5008. The examiner can normally be reached on Monday through Friday from 8:30 a.m. to 5:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan, can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Johann R. Richter/

Supervisory Patent Examiner, Art Unit 1616